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25 OCT 1985

PATENTS FORM No. 1/77 (Revised 1982)

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## REQUEST FOR GRANT OF A PATENT

8526408

THE GRANT OF A PATENT IS REQUESTED BY THE UNDERSIGNED ON THE BASIS OF THE PRESENT APPLICATION

I	Applicant's or Agent's Reference (Please insert if available)	JHFB/B1943
II	Title of Invention	CHEMICAL PROCESS
III	Applicant or Applicants (See note 2)	
	Name (First or only applicant)	Beecham Group p.l.c.
	Country	United Kingdom
	State	ADP Code No.
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	Name (of second applicant, if more than one)	
	Country	State
	Address	
IV	Inventor (see note 3)	(a) The applicant(s) is/are the sole/joint inventor(s) or (b) A statement on Patents Form No 7/77 is/will be furnished
V	Name of Agent (if any) (See note 4)	J.H.F. Blake
		ADP CODE NO
VI	Address for Service (See note 5)	
	Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey, KT18 5XQ, England	
VII	Declaration of Priority (See note 6)	
	Country	Filing date
		File number
VIII	The Application claims an earlier date under Section 8(3), 12(6), 15(4), or 37(4) (See note 7)	
	Earlier application or patent number	and filing date

IX Check List (To be filled in by applicant or agent)

- |   |  |
|---|--|
| A The application contains the following number of sheet(s) | B The application as filed is accompanied by:-       |
| 1 Request ..... 1 ..... Sheet(s)                            | 1 Priority document .....                            |
| 2 Description ..... 11 ..... Sheet(s)                       | 2 Translation of priority document .....             |
| 3 Claim(s) ..... - ..... Sheet(s)                           | 3 Request for Search .....                           |
| 4 Drawing(s) ..... - ..... Sheet(s)                         | 4 Statement of Inventorship and Right to Grant ..... |
| 5 Abstract ..... - ..... Sheet(s)                           |  |

X It is suggested that Figure No ..... of the drawings (if any) should accompany the abstract when published.

XI Signature (See note 8)  J.H.F. Blake Chartered Patent Agent,  
Agent for the Applicants

NOTES:

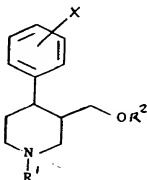
- This form, when completed, should be brought or sent to the Patent Office together with the prescribed fee and two copies of the description of the invention, and of any drawings.
- Enter the name and address of each applicant. Names of individuals should be indicated in full and the surname or family name should be underlined. The names of all partners in a firm must be given in full. Bodies corporate should be designated by their corporate name and the country of incorporation and, where appropriate, the state of incorporation within that country should be entered where provided. Full corporate details, eg "a corporation organised and existing under the laws of the State of Delaware, United States of America," trading styles, eg "trading as xyz company", nationality, and former names, eg "formerly (known as) ABC Ltd." are not required and should not be given. Also enter applicant(s) ADP Code No. (if known).
- Where the applicant or applicants is/are the sole inventor or the joint inventors, the declaration (a) to that effect at IV should be completed, and the alternative statement (b) deleted. If, however, this is not the case the declaration (a) should be struck out and a statement will then be required to be filed upon Patent Form No 7/77.
- If the applicant has appointed an agent to act on his behalf, the agent's name and the address of his place of business should be indicated in the spaces available at V and VI. Also insert agent's ADP Code No. (if known) in the box provided.
- An address for service in the United Kingdom to which all documents may be sent must be stated at VI. It is recommended that a telephone number be provided if an agent is not appointed.
- The declaration of priority at VII should state the date of the previous filing and the country in which it was made and indicate the file number, if available.
- When an application is made by virtue of section 8(3), 12(6), 15(4) the appropriate section should be identified at VIII and the number of the earlier application or any patent granted thereon identified.
- Attention is directed to rules 90 and 106 of the Patent Rules 1982.
- Attention of applicants is drawn to the desirability of avoiding publication of inventions relating to any article, material or device intended or adapted for use in war (Official Secrets Acts, 1911 and 1920). In addition after an application for a patent has been filed at the Patent Office the comptroller will consider whether publication or communication of the invention should be prohibited or restricted under section 22 of the Act and will inform the applicant if such prohibition is necessary.
- Applicants resident in the United Kingdom are also reminded that, under the provisions of section 23 applications may not be filed abroad without written permission or unless an application has been filed not less than six weeks previously in the United Kingdom for a patent for the same invention and no direction prohibiting publication or communication has been given or any such direction has been received.

- 1 -

CHEMICAL PROCESS

This invention relates to a novel chemical process for preparing aryl-piperidine carbinol ethers and to novel intermediates used in that process.

British patent no. 1422263 and US patent no 4007196 disclose compounds of formula A



A

in which  $R^1$  represents hydrogen, trifluoro ( $C_{1-4}$ ) alkyl, alkyl or alkynyl,  $R^2$  represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by  $C_{1-4}$  alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl, and  $X$  represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio, or aralkyloxy.

The compounds of formula A are disclosed as having pharmacological properties that make them useful as anti-depressants.

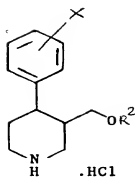
Among compounds of formula A in which  $R^1=H$ , a compound that has proved especially valuable is paroxetine ( $R^1=H$ ,  $R^2=1,3$ -benzodioxyl,  $X=F$ ). More specifically, paroxetine is (-)-trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxy)methyl-piperidine.

In the above mentioned patents, compounds of formula A in which  $R^1=H$  may be obtained by hydrolysis of the corresponding compounds in which  $R^1$  is an acyl group. The de-acylation may be part of a de-alkylation step to remove an N-alkyl protecting group introduced before addition of the group  $R^2$  to the corresponding piperidine carbinol. More specifically, for the preparation of paroxetine (Examples 1 and 2 of US 4007196), an N-methyl compound ( $R^1=CH_3$ ) is reacted with phenyl chloroformate and the resultant compound ( $R^1=CO.OCH_3$ ) is hydrolysed with potassium hydroxide.

In a subsequent step, the compounds of formula A are converted into acid addition salts of the free base. US 4007196 discloses the formation of the maleic acid salt of paroxetine; GB 1422263 discloses the formation of hydrochlorides of other compounds in which  $R^1=H$ .

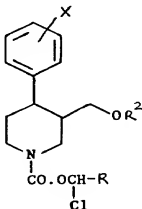
We have now discovered a new process for the preparation of compounds of formula A in which  $R^1=H$  by a de-acylation procedure which advantageously provides the desirable hydrochloride salt directly.

Accordingly, the present invention provides a process for the preparation of a compound of formula I



I

in which  $R^2$  and X are as defined for formula A, by de-acylating a compound of formula II

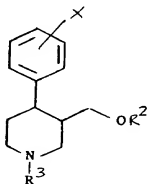


II

in which R is an alkyl group.

The de-acylation may be achieved by heating the compound of formula II in a lower alcohol e.g. methanol. Preferably R is a methyl group.

The de-acylation is advantageously carried out as the final step of a procedure for de-alkylating a compound of formula III

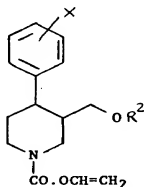


III

in which  $R^3$  is an alkyl group.

The replacement of  $R^3$  by  $R.CHClO.CO$  to convert the compound of formula III to the compound of formula II may be achieved by reacting the compound of formula III with  $\alpha$ -chloro-ethyl chloroformate in a solvent such as dichloroethane or toluene.

Alternatively, the compound of formula III may be reacted with vinyl chloroformate in a solvent such as methylene dichloride or toluene to obtain the intermediate of formula IV



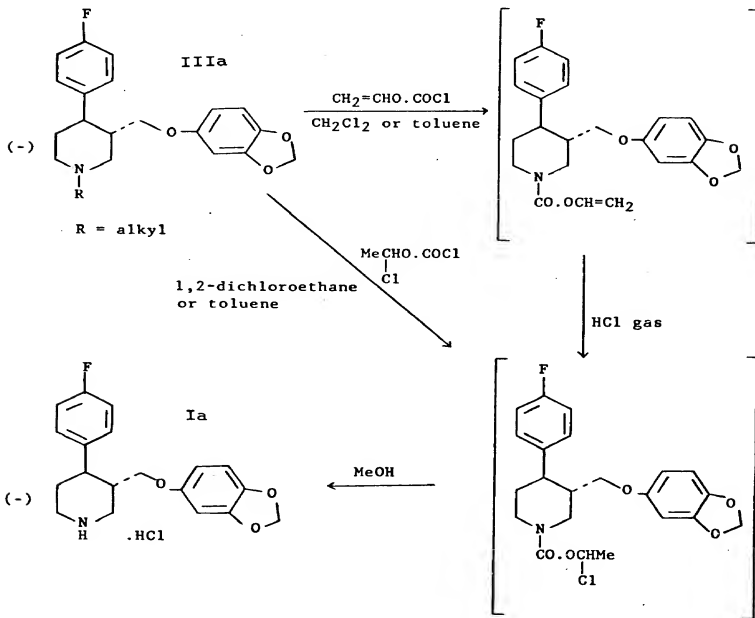
IV

which is then treated with  $HCl$ , preferably by passing  $HCl$  gas through the solution to obtain the compound of formula II.

An advantageous feature of the process of this invention is that the conversion of the compound of formula III into the compound of formula I can be carried out as a 'one-pot' process without isolating the intermediate of formula II or the intermediate of formula IV if the alternative route is followed.

The compounds of formula III may be prepared by the procedures set out in GB 1422263 and US 4007196.

Advantageously, the process of the present invention is used for the de-alkylation of a compound of formula IIIa to obtain paroxetine hydrochloride of formula Ia. This procedure is illustrated in the following reaction scheme.





The intermediates having the general formulae II and IV given above are novel compounds. They form part of the present invention, together with the processes for their preparation described herein.

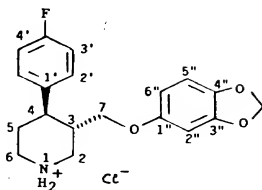
The present invention is illustrated by the following Examples; Examples 1 and 2 showing the route formula III-IV-II-I, Example 3 and 4 the route III-II-I. Temperatures are in °C.

Example 1

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylene-  
dioxypyhenoxy)methylpiperidine hydrochloride

Vinyl chloroformate (6.42ml) was dissolved in 2ml dry methylene dichloride. The solution was cooled to 0° and the reaction flask purged with nitrogen. A solution of (-)-trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxy)methyl-N-methylpiperidine (20g) in 52ml of dry methylene dichloride was added to the vinyl chloroformate solution over 30 minutes keeping the temperature below 0°. The mixture was allowed to warm to ambient temperature and stirred for 3 hours. The solution was then heated to reflux at 35° for a further 1 hour and cooled to -20°. Dry hydrogen chloride gas was bubbled into the solution for about 1 hour and the mixture allowed to stir at ambient temperature for 1 hour. Methanol (50ml) was added to the solution and the mixture heated under reflux for 1 hour, followed by addition of charcoal (4.5g) to the hot solution. Charcoal was filtered off after 10 minutes and the solvents removed in vacuo to give the crude product (21.4g). The solid was dissolved in isopropyl alcohol (140ml) and the solution filtered. The clear filtrate was cooled to 0° and seeded to allow the product to crystallise. After several hours at 0° the white solid was filtered off and the product slurried in water (30ml), filtered off, washed with water and dried to give the hydrochloride salt (15.8g, 74.1%).

<sup>1</sup>H-n.m.r. (270 MHz, DMSO-d<sub>6</sub>)



<u>δ</u>	<u>Multiplicity</u>	<u>Assignment</u>	
9.50	s, br, exch.	NH <sub>2</sub> <sup>+</sup>	2H
7.27	dd, <sup>4</sup> J <sub>HF</sub> =6Hz	2'	2H
7.17	dd, <sup>3</sup> J <sub>HF</sub> =9Hz	3'	2H
6.75	d	5''	1H
6.50	d	2''	1H
6.20	dd	6''	1H
5.94	s	O-CH <sub>2</sub> -O	2H
3.61	dd}	7	2H
3.53	dd}		
3.50	m	2 eq	1H
3.39	d, br	6 eq	1H
3.03	ddd	6 ax	1H
2.97	dd	2 ax	1H
2.90	ddd	4	1H
2.58	m	3	1H
2.10	ddd	5 ax	1H
1.85	d, br	5 eq	1H

Example 2

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxy)methylpiperidine hydrochloride

The reaction described in Example 1 was repeated substituting 100ml of sodium dried toluene for 52 ml of dry methylene chloride. (-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxy)methyl-N-methylpiperidine (20g) was converted to 16.5g of the hydrochloride salt in a yield of 77.4%.

The  $^1\text{H-n.m.r.}$  spectrum was identical to that of the Example 1 product.

Example 3

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxy-  
phenoxy)methylpiperidine hydrochloride

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxy-  
phenoxy)methyl-N-methylpiperidine (10g) and N,N,N',N'-  
tetramethyl-1,8-naphthalenediamine (0.3g) were  
dissolved in 40ml of dry 1,2-dichloroethane (EDC) and  
the solution cooled to -3°.  $\alpha$ -Chloroethyl  
chloroformate (3.22ml) in 5ml of dry EDC was added to  
the cold solution over 15 minutes. The mixture was  
stirred for 20 hours at ambient temperature and then  
heated to reflux for 2 hours. Methanol (15ml) was  
added to the solution and the mixture was refluxed for  
a further 2 hours. The mixture was washed with 20ml of  
1N hydrochloric acid and the phases were allowed to  
separate. The organic layer was evaporated to dryness  
and the residue was dissolved in isopropyl alcohol  
(60ml). The hot solution was treated with charcoal  
(2g) and alumina (1.5g), stirred for 5 minutes and  
filtered hot. The clear solution was seeded and cooled  
to 0° for 18 hours. The white crystalline solid was  
filtered off and the wet product slurried in water  
(20ml). The solid was filtered off, washed with water  
and dried to give the hydrochloride salt (7.9g, 74.1%).

The  $^1\text{H-n.m.r.}$  spectrum was the same as that of the  
Example 1 product.

Example 4

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylene-  
dioxypheoxy)methyl-piperidine hydrochloride

(-)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxy-  
phenoxy)methyl-N-methylpiperidine (10g) was dissolved  
in 45 ml of sodium dried toluene and the solution  
cooled to 5°.  $\alpha$ -Chloroethyl chloroformate (3.22ml) in  
5ml of dry toluene was added to the cold solution over  
15 minutes. The mixture was stirred for 18 hours and  
methanol (15ml) was added to the mixture. The solution  
was stirred for 12 hours at ambient temperature. The  
solvent was then distilled off in vacuo and the residue  
dissolved in hot isopropyl alcohol (60ml). The hot  
solution was treated with charcoal (2g) and alumina  
(1.5g), stirred for 5 minutes, filtered and cooled to  
0° for 18 hours. The white crystalline solid was  
filtered off, washed with a little isopropyl alcohol  
and the solid slurried in water (20ml). The solid was  
filtered off, washed with water and dried to give the  
hydrochloride salt (9.8g, 92%).

The  $^1\text{H-n.m.r.}$  spectrum was identical to that of the  
Example 1 product.